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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,570	05/23/2000	Francois Arminjon	MBHIB00-210	9141

7590 02/07/2005

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,570	ARMINJON ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-27 and 29-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,24-27 and 29-44* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 8, 2004 (originally November 12, 2004, non-compliant amendment) has been entered. Claims 21-27 and 29-44 are pending and under examination.

Claim Rejections - 35 USC § 103

2. Claims 21, 22, 24-27, 29-38, and new claims 39-44 are rejected under 35 U.S.C. 103(a) as obvious over Petre *et al.* (WO98/24148, herein, "Petre") in view of Arminjon *et al.* (AU708777, herein, "Arminjon"). This rejection has been previously made with respect to claims 21-27 and 29-38. Claims 36 and 37 have been amended to recite a method for conferring protection against all of the pathogens present in claims 36 and 37, respectively. Previously, claims 36 and 37 were drawn to a method for conferring protection against one or more of the pathogens present in claims 36 and 37, respectively. This new limitation in claims 36 and 37 does not alter the rejection of record because protection against all of the recite pathogens is expected in view of the combination of Petre and Arminjon for reasons of record.

New claims 39-44 are included in this rejection because the claims are drawn to embodiments that are encompassed by the prior art of record. Claims 39-44 are drawn to

methods of stimulating an immune response and conferring protection against various diseases, particularly in human infants. The vaccines of Petre and Arminjon, and the combination of the references, disclose vaccines for human infants (see Petre, claims 29-31 and Arminjon, page 8, lines 4-13). Therefore, the invention as a whole remains obvious over Petre in view of Arminjon. (See the Examiner's Answer for a summary of the rejection of record, mailed June 10, 2004.)

Response to Arguments

3. Applicant maintains that the Office has failed to clearly and with particularity identify the teachings or suggestions in the prior art to make the presented claimed methods and compositions comprising each of the recited antigens as required. Applicant points to several case law citations to support the requirement that the Office identify all of the components of the claimed invention and/or suggestions in the prior art regarding the claimed invention. The case law citations are directed to the general requirements of the Office in establishing a *prima facie* obviousness rejection, but the citations are not specific to any arguments in particular.

Applicant's substantive arguments are primarily directed to the following:

- Applicant maintains that the combination of Arminjon and Petre do not suggest adsorbing tetanus toxoid and diphtheria toxoid onto an aluminum salt before being mixed with other components. The Office relies on Petre's teachings (Petre, page 9, lines 1-3) to support the suggestion to adsorb components such as tetanus toxoid and diphtheria toxoid onto aluminum hydroxide (AH) or aluminum phosphate (AP) prior to mixing with other

components. Applicant argues that these teachings are limited to vaccines containing Hepatitis B surface antigen (HBsAg).

- In response, the Office recognizes that the teachings of Petre are all in the context of a vaccine that contains HBsAg (Petre, abstract). However, instant claims 21, 22-27 and 29-44 are not limited to the components listed in the claims because the method recites "comprising". In the claims' broadest reasonable interpretation, claims 21-27 and 29-44 require that all of the components listed be present in addition to anything else, which may include HBsAg. This is a reasonable interpretation of the claims because instant claim 25 recites HBsAg.

- Applicant also argues that Petre requires that all components of the vaccine be adsorbed onto an adjuvant, while Applicant's invention does not require the adsorption of all components onto an adjuvant. Applicant argues that Petre teaches away from the embodiment claimed in claim 23, wherein inactivate polio virus (IPV) is mixed with other components without being adsorbed onto an aluminum salt.

  - In response, the Office acknowledges that Petre suggests that in general, all of the vaccine components be adsorbed to AH or AP (see Petre, abstract and pages 8-9). However, the claims are not limited to adsorption of tetanus toxoid and diphtheria toxoid to AH or AP. In the claims' broadest reasonable interpretation, claims 21, 22, 24-27 and 29-44 require that all of the method steps listed be present in addition to anything else, which may include adsorption of the components to an adjuvant. This is a reasonable interpretation because instant claim 22 is drawn to

an embodiment wherein other vaccine components are adsorbed to an aluminum salt.

- Claim 23 is an exception because it requires that IPV not be adsorbed onto an aluminum salt. In this matter, Applicant's arguments have been considered persuasive. Therefore, claim 23 is not included in the prior art rejection and is free of the prior art of record.

- Applicant maintains that the combination of Arminjon and Petre does not suggest preparing the Hib conjugate in a phosphate buffer before mixing with the other components. The Office has relied on Arminjon, page 6, lines 33-40 to support the teaching that PRP-T is prepared in a phosphate buffer solution prior to mixing with other components. Applicant argues that this passage is primarily concerned with whether anions should be added to the aluminum complex before or after PRP-T, not whether PRP-T should be added to a phosphate buffered solution before the addition of other antigens in a multivalent vaccine.

  - In response, the Office recognizes that Arminjon teaches that the addition of the anions (phosphate and carbonate ions) relates to the modification of the aluminum complexes. However, Arminjon teaches what is required by the instantly claimed invention: PRP-T conjugate in a solution containing the chosen anions before contacting them with the adjuvant (page 6, lines 33-39). This process would obviously need to be done before adding the PRP-T component (adsorbed to the aluminum salt) to the rest of the vaccine components. Therefore, while Arminjon's teachings are more concerned with the anion/aluminum interaction,

the suggestion to mix PRP-T with anions ultimately prior to mixing with other components is suggested. The fact that Arminjon performs an additional step of adsorbing the PRP-T to aluminum is irrelevant, because of the broad claim language allows for other method steps.

- Applicant also argues that the ordinary artisan would not have had a reasonable expectation of successfully combining all of the antigens of the present claims to arrive at a composition having efficacy for each of its constituents. Applicant points to Arminjon, examples 12 and 13 which discloses the vaccination of mice with a multivalent vaccine. Arminjon reports that the PRP-T response was "satisfactory" in mice. Applicant argues that Arminjon fails to provide antibody titer data for any of the antigenic components used in the multivalent vaccine composition administered to mice.
  - In response, the combination of Arminjon and Petre uses the same amounts of antigen as Applicant's vaccine. The deficiencies of Petre were accounted for in the Arminjon reference, which disclosed the specific amounts of antigens used. Although Arminjon does not comment on the protective ability of the vaccine in Example 13, one would expect the immune response to be stimulated against the different antigens and a protective response in the combined method. One would expect a protective response because Petre's use of adsorption to AH/AP increases the stability of the antigen components. Increased stability would lead one of ordinary skill to expect a greater immune response.
- Applicant points to three literature references that discuss the difficulties in combining vaccine components into one composition. Eskola (*J. Infect. Dis.*, 1996, Vol. 174, Suppl.

3:S302-305) teaches that interference of different antigens in a combined vaccine must be considered carefully. In particular, Eskola expects interference between Hib, diphtheria, tetanus and pertussis antigens in the new DTPa-Hib combined vaccines. Eskola *et al.* (*The Lancet*, 1996, 348:1688-1692) teaches that the mixture of DTPa, IPV and Hib interferes with the primary antibody response to poliovirus antigens and Hib antigens. Applicant also points to Bell *et al.* (Vaccine, 1998, 16:637-642) which discloses a combination vaccine of DTPa adsorbed with aluminum hydroxide and mixed with PRP-T, which when administered, showed a decrease in Hib antibody titers compared to PRP-T administered separately. Applicant analyzes the antibody titers disclosed in Bell and concludes that the reduction of Hib antibody titers in various Hib vaccine that have been combined with acellular pertussis. Notably, Applicant points out that the presently claimed vaccine manifested the same level of Hib seroprotection as Bell's disclosed vaccine, despite the increased number of valencies in the instant vaccine. Applicant concludes that Applicant's vaccine's results could not have been anticipated with any reasonable expectation of success. Applicant argues that one of ordinary skill would expect that an increased number of valencies would decrease the effectiveness of each valancy. Applicant's case law citation regarding unexpected results in overcoming an obviousness rejection is noted.

- In response, the Office has considered the two Eskola references and the Bell reference with regard to their teachings on the effect of combining multiple valencies. It is noteworthy that only the Bell reference uses the adsorption technique with an aluminum salt. The Eskola *et al.* reference uses an aluminum

salt in the vaccine composition, but it was not adsorbed to any antigens in particular. Therefore, the only reference that applies in this context is the reference that includes adsorption of antigen to an aluminum salt, the Bell reference. The Bell reference does not offer a conclusive comment on the antibody titer required to provide protection against Hib. Bell only suggests that the Hib antibody titer (standard) for continued protection following immunization be raised.

- Further, the Office has considered Applicant's "unexpected results", namely, the seroprotective level of Hib antibody that is exhibited when administered a vaccine with numerous valancies. The unexpected results are directed to a particular level of antibody titer against a particular antigen. Because the combination of the Petre and Arminjon reference has a reasonable expectation of success, one would have achieved the same results that Applicant achieved. Had Applicant established that the combined vaccine would not have worked to stimulate an immune response or induce protection, the obviousness rejection would not stand. However, Applicant has failed to establish that one would expect the combined vaccine of Petre and Arminjon to fail. (The Bell reference does not indicate failure, merely a decreased antibody titer to a specific antigen.) Therefore, the unexpected results of Applicant's vaccine would have been achieved by one of ordinary skill in the art because it would have been obvious to combine the teachings of Petre with Arminjon.

Conclusion

4. No claim is allowed. Claim 23 is objected to for depending from rejected claim 21.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
February 1, 2005